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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

01/17/96

☑ This application has been examined ☑ Responsive to communication filed on 5/22/95 ☑ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~days~~ from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☑ Claims 4-6, 8, 20-26 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☑ Claims 1-3, 7, 9-19 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 4-6, 8, 20-26 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Status of the claims

Currently, claims 4-6,8,20-26 are pending for action. Claims 1-3,7,9-19 have been cancelled.

Specification

1. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the mature tissue factor protein of Figure 2 and that having a deletion of the transmembrane domain. See MPEP section 706.03(n) and 706.03(z). The scope of the claiims is not commensurate with the enablement provided by the original disclosure with regard to the extremely large number of proteins broadly emcompassed by the claims. Furthermore, the claims broadly encompass significant number of inoperative species.

The specification fails to provide guidance regarding sequence similarity (or lack thereof) with tissue factor from other tissue sources or from other animals. Guha, et al discose that there is poor immunological cross-reactivity of tissue factor proteins between human and other animal sources. This suggest that substantial sequence variation between animal species exist and it would have been unpredicatable whether the disclosed DNA would be useful in cloning the tissue factor protein of other animal sources. Thus, it would require undue experimentation to clone other natural forms of tissue factor protein.

Additionally, since the amino acid sequence of a protein determines its structural and functional properties, pedictability of which changes can be tolerated in a protein's amino acid sequence and still

retain similar activity/utility requires knowledge and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which proteins' structure relates to its function. Prediction of protein structure from mere sequence data of a single protein and utilizing the predicted structural determinations to specified functional aspects of the protein is well outside the realm of routine experimentation. Therefor, it is unpredictable whether any of the modifications to which the claims are drawn would be workable in the instant protein, especially in view of the non-conservative nature of the changes.

It is not routine in the art to screen for multiple substitutions or modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. Pongor (1987, Methods in Enzymology) teaches that it is expensive and time consuming to make amino acid substitutions at more than one position, even in a particular region of the protein in view of the manifold possibities for change in structure and the uncertainty as to what utility will be possessed by such muteins. The teaching of Pongor further evidences that the experimentation required to make up for what the disclosure and prior art lacks is undue in its teaching that the quantity of experimentation is clearly prohibitive. The practioners of the art are not prepared to test and screen recombinant protein muteins having multiple substitutions as a routine means of determining other similar analogs or muteins.

The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does not disclose the following: (A) the general tolerance to modification and extent of such tolerance; (B) specific positions and regions of the

sequence(s) which can be predictably maodified and which regions are critical to activity; (C) what fragments of the extracellular domain can be made which retain the biological activity of the intact protein; and (D) the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Finally, "tissue factor protein" is merely functionally defined as any protein capable of correcting various bleeding disorders and it would clearly require undue experimentation to support the scope of the proteins encompassing an essentially infinite number of possible structures and amino acid sequences including those unrelated to the disclosed human sequence. Applicant has failed to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the broad scope of the claims including any number of insertions, deletions or substitutions and fragments of any size. Without such guidance, the changes which can be made in the protein structure and still maiintain activity/utility is uncessarily, and improperly, extensive and undue.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as it is now claimed. The newly added limitation to "from amino acid one to less than amino acid 263" is directed to a new subgenus that was not originally described.

Claim Rejections - 35 USC § 112

3. Claims 4-6,8 and 20-26 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the mature tissue factor protein of Figure 2 and the protein having a deletion of the transmembrane domain. See M.P.E.P. §§ 706.03(n) and 706.03(z).

4. Claims 20-26 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The specification did not explicity or implicityly describe an encoded tissue factor protein having both the transmembrane and cytoplasmic region (and/or portions thereof) deleted. Deletion of one or more amino acids or regions within a proein involves the C-terminal to the deletion and this deletion does not simply fall off but remains part of the protein covalently joined where the amino acid(s) or region were deleted.

Response to Amendment

5. Applicant's arguments filed in the parent case SN 08/167,715 have been considered herein but they are not deemed to be persuasive.

Rejection of claims 20-26 under 35 USC 112, first paragraph

The original specification fails to support the new subgenus of "from amino acid one to less than amino acid 263". The specification did not explicity or implicityly describe an encoded tissue factor protein having both the transmembrane and cytoplasmic region (and/or portions thereof) deleted.

Deletion of one or more amino acids or regions within a proein involves the C-terminal to the deletion and this deletion does not simply fall off but remains part of the protein covalently joined where the amino acid(s) or region were deleted.

Rejection of claims 4-6,8 and 20-26 under 35 USC 112, first paragraph

The claims are sufficiently broad to include all deletion fragments and tissue factor protein down to one amino acid in length. Without guidance regarding which shorter fragments of the extracellular domain and the extent of fragmentation of the extracellular domain which can be tolerated it would require undue experimentation to determine such since one skilled in the art would not have the expectation of success in obtaining the fragments,especially substantially smaller fragments.

Applicant agrue that the claims are limited to "human" tissue factor. Applicant claims fails to positively support such assertion. Only claims that specify the sequence inherent to human tissue factor might support applicant's assertion.

Arguments directed to deletions and activity have been considered, however examiner maintains that the arguments does not support the broad scope of all deletions. Examiner agrees that the transmembrane deletion is fully supported and was known in the art at the time of the invention. Deletions within the active portion (extracellular domain) would have been unpredictable since the protein function depends upon its structure. Lacking specific guidance, deletion of one to ten amino acids within the active region would have had unpredictable effectsw and there was no expectation of success. Applicant cites that tissue factor as small as 209 amino acids has "subsequently" been reported to be active in a factor VII assay. The reference was published subsequent to the filing date

and the reference fails to establish that undue experimentation was not required to isolate the factor. Moreover, at the time of when the invention was made, applicant's reference would have provided little guidance to the skilled artisan regarding where other deletions could be made or the extent of such deletions in the extracellular domain.

Applicant's cite publications published after the date of the invention which show the rather large divergence in amino acid sequence identity between the human tissue factor protein and those of bouve, mouse and rabbit. The publications teachings cannot support the instant disclosure since these were published after the date of the invention. Further, since the properties of the proteins having such divergence would likely have been different due to the presence of at least 25% different amino acids, it is unpredictable whether the same or obviously similar purification procedures could have produced them. Additionally, mouse and rat DNAs would not hybridize to the human sequence since the DNA sequence identity with the human sequence is 62% and 61%, respectively. (See Lathe for teaching of sequence homology and hybridization.) Applicants contends that all claimed forms have been made and reported in the literature to have biological activity and that, with sequence in hand, it would have been routine to modify the sequence. These arguments are allegations unsupported by evidence and are not persuasive. All considerations must be made with data and facts that were known at the time of the invention. Applicants dislcosed only one sequence from one organism and whether there was sufficient homology with any other organisms was unknown and those skilled in the art would not have had the resonable expectation of success.

Conclusion

6. This is a continuation application under 37 CFR 1.62 of applicant's earlier application S.N. 167,175. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Applicants remarks regarding the allowance of the divisional application and its' placement in an interference have been noted. In order for the application to be joined with the pending interference, the instant application should have one claim indicated to be allowable. Furthermore, all applications not in interference having the same inventor or common assignee should be prosecuted to the furthest extent and the outstanding rejections directed to the scope and new matter issues should be resolved prior to a determination regarding whether the claims are drawn to a divisible distinct invention and/or whether the claims dominate matter claimed in the application involved inthe interference, or whether to join the instant application to the interference or to reject the instant claims over the count under 35 USC 102(g) and suspend the application pending outcome of the interference.

No determination with regard to the various possible actions is deemed appropiate at this time. See MPEP 2315.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J Isabella whose telephone number is (703) 308-4958. The examiner can normally be reached on Monday, Wednesday and Thursday from 9:00am to 4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Robert Wax, can be reached on (703) 308-4216.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID J ISABELLA
PRIMARY EXAMINER

DJI
JANUARY 4, 1996